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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/284,424 | 04/09/99 | ALBRECHT | H 5500-01-TMC |

HM22/0705

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| EXAMINER | |
|---|---|
| MAIER, L | |
| **ART UNIT** | **PAPER NUMBER** |
| 1623 | 8 |

**DATE MAILED:** 07/05/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/284,424 | Albrecht et al |
| **Examiner** | **Group Art Unit** |
| Leigh Maier | 1623 |

☒ Responsive to communication(s) filed on *amendment filed May 1, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claim**

☒ Claim(s) *1-8, 10-31, 34, 38-41, and 44-50* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-8, 10-31, 34, 38-41, and 44-50* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

Howard C. Lee

Howard C. Lee
Primary Examiner
Art Unit 1623

*— SEE OFFICE ACTION ON THE FOLLOWING PAGES —*

## DETAILED ACTION

### *Status of the Claims*

1. Claim 1 has been amended. Claims 9, 32*, 33, 35-37, 42, and 43 have been canceled. Claims 44-50 have been added. *It is noted that the amendment cancels claim 32, but the remarks refer to the cancellation of claim 31. It is not clear whether applicant meant to cancel 31, 32 or both. The examiner considers the following claims to be pending in the case: 1-8, 10-31, 34, 38-41, and 44-50 as per the amendment.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The original disclosure presents a genus of compounds with several independent variables and no limits on what particular species are allowed. A proviso has been added in amended claim 1 that excludes three particular species and introduces some dependency between variables. See (a)-(d) of the proviso, page 10 of amended claim 1. This specific

dependency relationship was not previously disclosed. Any negative limitation or exclusionary proviso must have basis in the original disclosure.

### *Claim Rejections - 35 USC § 103*

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-8, 10-31, 34, 38-41, and 44-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Prasad et al (Bioorg. & Med. Chem. Lett., 1995) in view of Mjalli et al (Bioorg. & Med. Chem. Lett., 1994), Dolle et al (EP 0623592), and Chapman (US 5,430,128) .

The present claims are drawn to compounds of formula I, recited to be inhibitors of interleukin converting enzyme (ICE). Then enzymes are also known as ~~caspases~~ caspases. The non-variable core of the compounds is an aspartate α-oxymethyl ketone, with variable $R^1$ and $R^2$ on either end of the core formula. Depending on the particular $R^2$, the resulting compound is an aspartate α-(arylacyl)oxymethyl ketone or an aspartate α-(acyl)oxymethyl ketone.

Prasad et al teach the structural requirements for ICE inhibitors. The most potent ones are α-(arylacyl)oxymethyl ketones in which the group attached to the aspartate amino group (corresponding to $R^1$ in formula I) is a benzyloxycarbonyl protecting group or one or two

hydrophobic amino acids in sequence. The amino acids may be protected or unprotected. Prasad et al teach aryl groups attached directly to the carbonyl (corresponding to $R^2$ in formula I) with no intermediate methylene groups.

Mjalli et al teach similar α-(arylacyl)oxymethyl ketones as ICE inhibitors with an hydrophobic amino acid and an amino acid isostere attached to the aspartate amino group (corresponding to $R^1$ in formula I). The "$R^2$" group is a phenyl ring connected to the core carbonyl by a $C_2$ methylene chain. (See reaction scheme on page 1966 and compound 4c in Table 1). Dolle et al teach similar compounds allowing for a $C_0$-$C_6$ connection between the carbonyl and the aryl group.

Chapman et al teach similar α-(arylacyl)oxymethyl ketones as ICE inhibitors with three amino acids (unlimited in their hydrophobicity/hydrophilicity) attached to the aspartate amino group (corresponding to $R^1$ in formula I). In this reference, the "$R^2$" group is not limited to aryl or ara-alkyl. Also taught in this reference is the use of these compounds in the treatment of disorders related to the activity of interleukin-1.

It would have been obvious for the skilled artisan to have prepared compounds of formula I as ICE inhibitors and as treatments for disorders related to the activity of this enzyme. One having ordinary skill in the pharmaceutical arts would have been motivated to use the well-known α-(arylacyl)oxymethyl ketone template for synthesizing ICE inhibitors to prepare new drug treatments for ICE-related illnesses and syndromes.

The examiner acknowledges that claims 34 and 38-41 were previously deemed allowable in paper no. 4. However, after further consideration of the state of the art in designing inhibitors for ICE as discussed above, the allowability of these claims is withdrawn, and they are rejected as being obvious over the prior art.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (703) 308-4525. The examiner can be reached on Monday through Friday from 8:00 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Geist, can be reached at (703) 308-1701. The official fax number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

LCM

June 30, 2000

Howard C. Lee

Howard C. Lee
Primary Examiner
Art Unit 1623